REMARKS/ARGUMENTS

With entry of this amendment, claims 1-2, 6-8, 12, 14-17, and 32 are pending in the above-identified application. Claim 13 is canceled, claim 7 is amended, and claim 32 is added as set forth in detail below. No new matter is added. Applicants reserve the right pursue claims of original scope in a related, co-pending application. Examination and reconsideration of all pending claims is respectfully requested.

Claim Amendments

Claim 13, which recites administration of peptide antigen and non-viral vector "simultaneously as a mixture," has been canceled without prejudice to eliminate any inconsistency with independent claim 1, which recites administration "separately to closely adjacent sites."

Claim 7 has been amended to further expedite prosecution of the instant application by deleting recitation of an "HIV antigen."

New independent claim 32 has been added to recite a specific embodiment of the subject matter canceled from claim 7. New claim 32 recites a method substantially as set forth in claim 1 where the epitope(s) are one or more CTL epitope(s) of HIV. Support for this new claim is found in the specification at, for example, page 9, lines 6-8; and page 16, lines 8-17.

Rejections under 35 U.S.C. § 112, first paragraph

Claim 7 stands rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled by the specification. In particular, the Examiner contends that the specification does not enable one of ordinary skill in the art "how to elicit an immune response in a subject comprising administering in vivo a peptide or protein antigen from an HIV protein comprising one or more T cell epitopes with a non-viral vector comprising a polynucleotide encoding at least one of a B7-1, B7-2 or B7-3 co-stimulatory molecule." While this rejection is obviated in view of the

amendment to claim 7 deleting reference to an HIV antigen, Applicants will address the rejection as it may be applied to new claim 32.

First, in response to the Examiner's stated position that "the disclosed use for the claimed method is to vaccinate and treat," Applicants note that (1) the "how to use" prong of 35 U.S.C. § 112 is satisfied where the specification enables at least one disclosed use, *see, e.g.*, MPEP § 2107.02 (I), and (2) as previoiusly set forth in Applicants' response of 5/23/05, enablement under § 112 must be "evaluated against the claimed subject matter," MPEP § 2164.08 (emphasis provided). Here, new claim 32 recites the use of "eliciting an immune response" to an HIV antigen in a subject. *See* claim 32. The elicitation of the immune response comprises separate administration of a peptide or protein antigen encoding one or more HIV CTL epitopes and a vector encoding B7-1, B7-2, or B7-3 to closely adjacent sites. The Examiner does not contend that the specification does not enable elicitation of an immune response to an HIV antigen as recited in the claim. Further, the Examiner appears to accept Applicants' assertion that enhancement of an immune response (relative to administration of antigen alone) is a pharmacological activity achieved by the claimed method that constitutes an immediate benefit to the public. Instead, the Examiner relies on statements in the specification pertaining to use of B7 vector/protein antigen co-administration to "vaccinate and treat." To the extent, however, that the Examiner interprets vaccination and treatment as requiring "curing" or absolute "prevention" of HIV-induced AIDS, Applicants note that there is nothing recited in claim 32 requiring that such results be achieved. Accordingly, for the reasons above, enablement of the recited use for "eliciting an immune response" to an HIV antigen satisfies the "how to use" requirement, even if curing or prevention is not necessarily achieved.

Second, for essentially the reasons above, because claim 32 does not require elicitation of "protective immunity" to HIV, the Examiner's assertions regarding difficulties in developing an HIV vaccine for eliciting "protective immunity" are not relevant to enablement of the present claim. With particular regard to the Examiner's comments regarding the "gap between a vaccine candidate and product development" and "ethical concerns surrounding clinical trials," Applicants emphasize these alleged concerns are also not pertinent to determination of patentability. Neither the patent statutes nor the pertinent case law require that

a marketable product be developed in order to meet the requirements of 35 U.S.C. § 112, first paragraph. Nor is there any legal basis for asserting that "ethical concerns surrounding clinical trials" should support non-enablement of a claimed invention. To the contrary, as stated by the MPEP, "[t]he Office must confine its review of patent applications to the statutory requirements of the patent law. Other agencies of the government have been assigned the responsibility of ensuring conformance to standards established by statute for the advertisement, use, sale or distribution of drugs." MPEP § 2107.03.

Further, with respect to the Examiner's assertion that blocking B7 will "ameliorate the course of AIDS by slowing down the growth of HTLV-1 (HIV)-induced leukemias, ... teaching away from stimulating T cells in HIV infected patients," and while Applicants do not agree that this alleged teaching of U.S. 5,942,607 negates enablement of claim 7 as unamended, Applicants note that new claim 32 recites that the peptide or protein antigen comprises "one or more cytotoxic T lymphocyte (CTL) epitope(s) of HIV" (emphasis provided). Accordingly, claim 32 is directed to a method for activating CTLs, which are $CD8^+$. It was well-known as of the effective filing date that only $CD4^+$ T cells, and not $CD8^+$ T cells, are normally infectable by HIV. Therefore, any teaching in U.S. Patent No. 5,942,607 pertaining to amelioration of HIV-induced leukemias applies only to $CD4^+$ cells and not CTLs. For this reason, this aspect of the Examiner's rejection is obviated with respect to new claim 32.

In addition, regarding to the Examiner's citation to Letvin as allegedly teaching that antibody-based and traditional vaccine modalities may not be sufficient and that cell-mediated immunity will be essential, such a teachings directly supports enablement for new claim 32, which, by virtue of recitation of "one or more CTL epitope(s)," is indeed directed to a method for eliciting cell-mediated immunity and not antibodies. Accordingly, this aspect of the Examiner's rejection is also obviated by claim 32.

Therefore, for at least the reasons above as well as for reasons previously of record, and in view of the pertinent subject matter as presently recited in claim 32, Applicants believe claim 32 to be enabled by the specification under 35 U.S.C. § 112, first paragraph.

Withdrawal of the present rejection of claim 7, as it pertains to new claim 32, is respectfully requested.

Claim rejections under 35 U.S.C. § 103(a)

Claims 1, 2, 6-8 and 11-17 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,942,607 in view of Kaufmann *et al.*, alleged admitted prior art in the specification on page 37 at line 7-18, Rock *et al.*, U.S. Patent No. 5,738,852, WO 98/04705, the *CAPLUS* Accession No. 1998 (106018 summary of WO 98/04705), U.S. Patent No. 6,338,947, and U.S. Patent No. 6,045,802. This rejection has been maintained substantially as presented in the previous Office Action, with the addition of two newly cited references, namely, U.S. 6,338,947 and U.S. 6,045,802. Applicants maintain traversal of the instant rejection as set forth below.

First, it appears that the Examiner, in maintaining the instant rejection over Applicants' previous amendment and arguments of 5/23/05, has effectively "read out" an express limitation of the claims. The Examiner asserts that the "limitation 'closely adjacent' can be broadly interpreted to read on sites of undetermined distance since they can be functionally closely adjacent as disclosed in the instant specification." (Office Action dated 7/27/2005 at p. 5.) It appear that the Examiner relies on this assertion as a basis for ignoring the claims' recitation of "closely adjacent." In discussing the alleged teachings of the cited references in relation to the claims, the Examiner does not show where the cited art teaches or suggests separate administration to "closely adjacent" sites.

While Applicants agree that "closely adjacent," as recited in the claims, refers to a distance defined substantially in functional terms, the Examiner appears to accept, or at least does not refute, that "closely adjacent" does require some distance between the sites of administration. Indeed, this interpretation is consistent with the specification's disclosure, as required by the MPEP and pertinent case law. *See* MPEP § 2111 (stating that a reasonable interpretation of the claims "must also be consistent with the interpretation that those skilled in the art would reach" and citing *In re Cortright*, 49 USPQ2d 1464,1468 (Fed. Cir. 1999), in which

the court rejected the Board's interpretation of a claim as inconsistent with applicant's disclosure). The specification states, for example, that "typically, when the peptide or protein antigen and vector are administered separately, they are delivered to the same ***or*** closely proximate site(s) ...." (Specification at page 42, lines 24-26 (emphasis provided).) Accordingly, in view of the specification's reference to the "same" and "closely proximate" in the alternative, the ordinarily skilled artisan, reading the claims in light of the specification, would not reasonably interpret the term "closely adjacent" as including the "same" site. Instead, consistent with the specification, the skilled artisan would reasonably interpret "closely adjacent" as referring to different sites of administration of the vector and antigen at some distance therebetween and which otherwise meet the described functional constraints of "closely adjacent."

Applicants further note that the term "closely adjacent" is a limitation that must be fully considered by the Examiner is establishing a *prima facie* case under 35 U.S.C. § 103. In this regard, when the term "closely adjacent" is reasonably interpreted in a manner consistent with the specification to refer to different sites at some distance therebetween, as set forth above, none of the cited references, whether alone or in any combination, teach or suggest this limitation. The Examiner admits that U.S. 5,942,607 does not disclose administration to closely adjacent sites. (*See* Office Action dated 7/27/05 at p. 5.) The Examiner also admits that the U.S. 6,045,802 discloses using an "admixture" of vector encoding antigen and vector encoding B7. (*See id.* at p. 7.) Further, while the Examiner asserts that U.S. 5,738,852 discloses that "separate polynucleotides," encoding antigen and co-stimulatory molecule, can each be mixed with an excipient and administered, there is no teaching or suggestion in U.S. 5,738,852 of administration to "closely adjacent" sites as recited in the claims.

As to the Examiner's citation to U.S. 5,942,607 as allegedly teaching transfection of APCs with nucleic acid encoding B7 and sequentially pulsing with peptide antigen, Applicants respectfully request clarification as to where U.S. 5,942,607 contains this teaching. In any case, Applicants note that this reference does not actually demonstrate such nucleic acid transfection coupled with peptide pulsing, particularly in an *in vivo* context. Moreover, while transfection and pulsing *in vitro* might be expected to get the two agents into the same cell, it is

well-known that *in vitro* models are not necessarily predictive of *in vivo* results. Indeed, as of the effective filing date, the ordinarily skilled artisan would view *in vivo* administration of two agents (whether peptides, nucleic acids, or a combination of the two) as involving additional factors that affect diffusion and sequestration of the agents, and therefore uptake of the agents by cells. As evidence of this state of knowledge in the art, Applicants refer the Examiner to Shirai *et al.*, *J. Immunol.* 152:549-556, 1994 (attached hereto as Exhibit A). The study described by Shirai *et al.* showed that mixing a helper peptide and CTL epitope peptide and administering them as an admixture (thereby administering these agents at the same site) did not work to induce CTL activity. Instead, the peptides had to be covalently linked, or else physically linked by enclosure in the same microdroplets in incomplete Freund's adjuvant. (*See* Shirai *et al.* at p. 551, second column, first full paragraph; and p. 552, second column, last paragraph bridging to p. 553, first column. *See also id.* at Abstract.) This requirement for covalent or physical linkage suggests that the unlinked peptides, administered *in vivo* as an admixture, do not reach the same antigen presenting cells. (*See id.* at p. 553, first column (noting the requirement for proximity or presentation of the peptide determinants on the same cells).) Although this study deals with two peptides rather than a peptide and a DNA molecule, it demonstrates the basic principle that, unless two molecules are linked, there is not a reasonable expectation that these agents will be introduced into the same cell when injected *in vivo*, even if at the same site, let alone at separate but closely adjacent sites.

Therefore, for the reasons above, a *prima facie* case of obviousness has not been established with respect to the present claims. A *prima facie* case under 35 U.S.C. § 103 requires, *inter alia*, a showing of a teaching or suggestion of all limitations as recited in the claims, as well as a reasonable expectation of success. *See* MPEP §§ 2143.02 & 2143.03. In this case, the Examiner has not shown where the cited references teach or suggest administration of vector and antigen to separate sites that are "closely adjacent." Further, evidenced by Shirai *et al.*, there is no reasonable expectation of success that two agents administered *in vivo* will taken up by the same cell. Accordingly, withdrawal of the present rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

/for Brian W. Poor Reg. No. 32,928

Nicholas V. Sherbina
Reg. No. 54,443

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 206-467-9600
Fax: 415-576-0300
Attachment
NVS:seh
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